Sex Differences in Neural Correlates of ADHD Among Children and Adolescents

Undergraduate Research Thesis

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by

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a debilitating psychiatric condition characterized by symptoms of hyperactivity, impulsivity, and inattention. It exerts negative effects on persons affected, on their families, and within broader communities. The hyperactive-impulsive (HI) and combined (C) presentations portend development of both externalizing and internalizing psychopathology across the lifespan—trajectories of which often differ by sex. Both girls and boys with ADHD in childhood are vulnerable to developing oppositional defiant disorder (ODD) in childhood. Thereafter, however, males are vulnerable to conduct disorder (CD), substance use, and antisocial personality disorder (ASPD), whereas females are vulnerable to self-harm, suicidal behaviors, substance use, and borderline personality disorder (BPD). These trajectories can be explained in part through the lens of ontogenic process models, which consider how genetic, neural, and other biological vulnerabilities interact with environmental risk factors over time to alter neurodevelopment and canalize problematic behavior. This review details dysfunction in dopaminergic (DA) and serotonergic (5-HT) and noradrenergic (NA) systems that may underlie certain sex differences in ADHD and its progression. Gaps in knowledge are identified that should guide future research on developing and implementing treatments for ADHD among girls. Major findings illustrate that neural pruning, testosterone (in conjunction with monoamine oxidase [MAOA] gene expression), and the sex-determining region Y gene (SRY) contribute to differences in hypofunctioning DA systems among males versus females. In addition, expression of the 5-HT transporter gene (5HTTLPR) and estrogen levels during premenstrual syndrome (PMS) can contribute to dysregulation of the 5-HT system, leading to sex differences in ADHD symptoms. These findings suggest that sex divergences in neurochemical system function underlie at least some differences in ADHD expression.

Sex Differences in Neural Correlates of ADHD Among Children and Adolescents

Attention-deficit/hyperactivity disorder (ADHD) is a debilitating psychiatric condition with typical age-of-onset during childhood. ADHD affects intrapersonal, academic, social, and intellectual function (APA, 2013). Among other symptoms, ADHD is characterized by difficulties maintaining focus, constant fidgeting, impatience, and inability to stay seated relative to developmentally typical peers. Three presentations of ADHD are described in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (APA, 2013). These include the inattentive (ADHD-IN) presentation, which is characterized primarily by inattention; the hyperactive-impulsive subtype (ADHD-HI), characterized primarily by hyperactivity and impulsivity; and the combined subtype (ADHD-C). As I describe in later sections, considerable research suggests different pathophysiology for ADHD-IN, which affects boys and girls in equal proportions, than for ADHD-HI and ADHD-C (henceforth ADHD-HI/C), which affect far more boys than girls.

ADHD is most prevalent among children; estimates derived from primary care settings indicate that 4-12% of children ages 6-12 years meet criteria for some form of ADHD (Brown et al., 2001). In contrast, prevalence rates for adults range from 2-3%. In recent years, adult prevalence rates, which are likely underestimates, have been rising (see Beauchaine, Ben-David, & Bos, 2020; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). In addition, ADHD is often comorbid with learning disabilities; externalizing behavior disorders including oppositional defiant disorder (ODD), conduct disorder (CD), and substance use disorders (SUDs); as well as internalizing disorders including anxiety and depression (Bernfort Nordfeldt, & Persson, 2008; Wilens, Biederman, & Spencer, 2002).

Given the high prevalence of ADHD and its comorbidities with other psychiatric conditions,

personal and societal costs are difficult to overstate. Generally, such costs fall into three often inter-related categories: personal, family, and economic (Bernfort, Nordfeldt & Persson, 2008; Hakkaart-van Roijen et al., 2007). Personal costs of ADHD are perhaps most salient, and include difficulties in school, poor peer relationships, employment difficulties, financial distress, and problems with authority figures. Together, such effects contribute to the low self-esteem characteristic of ADHD (Bernfort et al., 2008; Wang, Huang & Jing, 2007).

ADHD is also associated with fewer years of schooling and lower scores on exams in academic contexts (Bernfort et al., 2008). Although ADHD was once thought to be a condition of childhood, symptoms persist into adulthood for more than 50% of those who are diagnosed (Wilens et al., 2002). Moreover, many boys with the ADHD-HI/C presentations develop increasingly severe externalizing disorders across development, including ODD, CD, SUDs, and antisocial personality disorder (ASPD). Economically, children and adolescents with ADHD are more dependent on and more costly to their families than children without ADHD (Bernfort et al., 2008; Barkley, 2020; Doshi et al., 2012). This results from a variety of factors including direct costs of treatment for both ADHD and comorbid disorders, as well as indirect costs through loss of work, lowered productivity, higher rates of drug abuse and criminality, and higher incidence of accidents (Matza, Paramore & Prasad, 2005). In the U.S., annual production loss due to ADHD is estimated to be $690 per affected male. Moreover, annual outpatient care costs are $4,929 for people with ADHD compared with $1,473 for controls (Bernfort et al., 2008). In 2012, overall costs to the U.S. education system for ADHD were between $15 million and $25 million (Ruland, 2012).

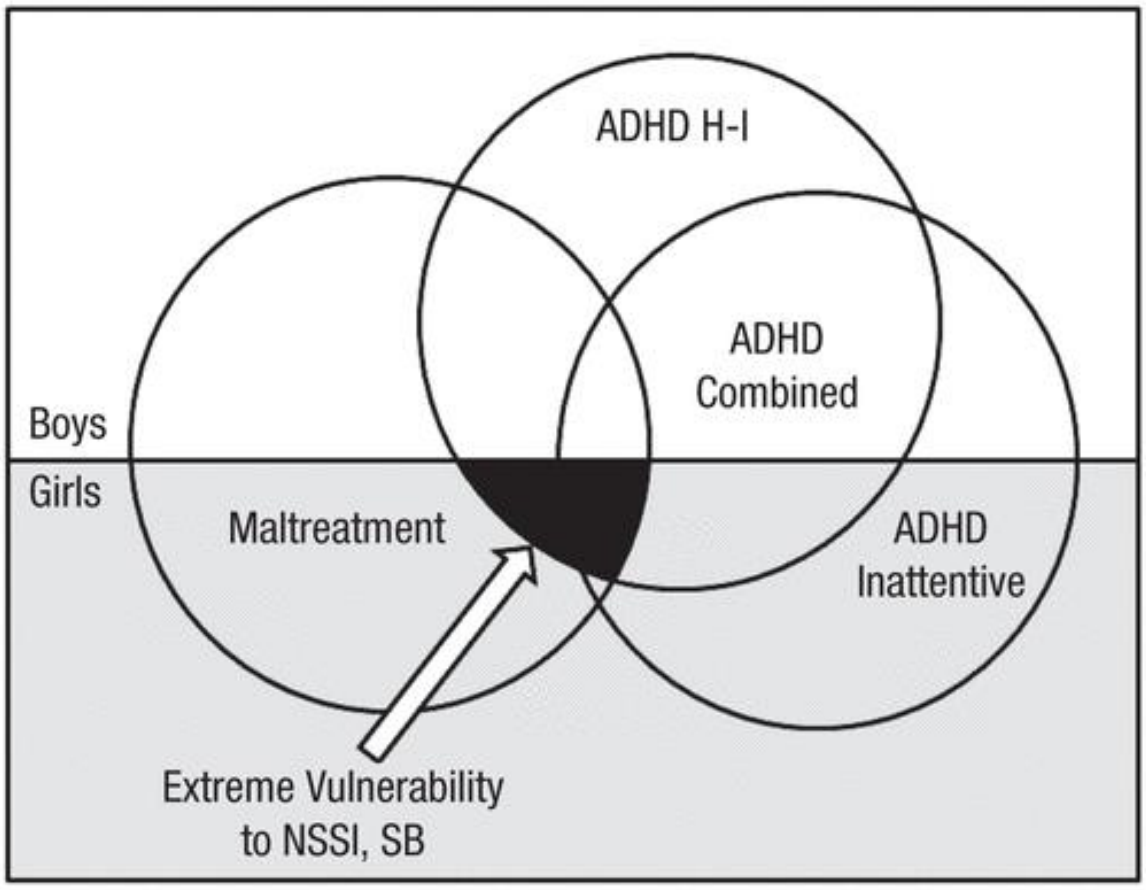
In addition, when controlling for other factors (e.g., other diagnoses, time driving), driver license loss is three times more common among those with ADHD compared to controls. ADHD

is also associated with underemployment, self-employment, and lower earnings (Stein, 2008). Although often overlooked, consequences for families are substantial. ADHD places a large emotional burden on supporting family members, causing higher levels of stress, exhaustion, and conflict (Wilens et al., 2002). More detailed discussion of costs associated with ADHD can be found elsewhere (e.g., Beauchaine, Ben-David & Bos, 2020; Beauchine, Gartner, & Hagen, 2000; Birnbaum et al., 2000; Le et al., 2014;).

Although most of the research listed above was conducted with primarily male samples, there is some research on ADHD pathways of girls. Like boys with ADHD, girls tend to develop internalizing symptoms and disorders. Unlike boys, however, 15-20% of girls with ADHD-HI/C in childhood eventually engage in nonsuicidal self-injury (NSSI; see Beauchaine, Hinshaw & Bridge, 2019). Among girls with ADHD who experience physical or sexual abuse, rates of NSSI rise to 50% (Allely, 2014; Beauchaine et al., 2019)—a phenomenon not observed among boys. Figure 2, shows how the intersection of various risk factors confers vulnerability to NSSI and suicidal behaviors among girls with ADHD.

Figure 1.

Vulnerability to nonsuicidal self-injury and suicidal behaviors as a function of intersecting risk factors. From Beauchaine et al. (2019).



As this discussion reveals, ADHD exacts many costs, and environmental risk factors influence its expression. Thus, ADHD is etiologically complex. Research addressing mechanisms underlying the disorder may shed light on factors that need to be addressed for early detection of risk and for treatment of specific populations, including girls vs. boys.

Differentiating Hyperactivity from Inattention

To develop optimal treatments for ADHD, it is important to understand its etiology, including genetic, neural, neurocognitive, and environmental mechanisms across the lifespan

(Beauchaine, Neuhaus, Brenner & Gatzke-Kopp, 2008). As alluded to above, it is essential to differentiate ADHD-IN from ADHD HI/C. A growing research base suggests that the form of inattention observed in ADHD-IN (sluggish cognitive tempo; see below) is different in kind from the inattention observed in ADHD-HI/C, which arises secondarily to hyperactivity-impulsivity (Beauchaine, Zisner & Sauder, 2017; Lee, Burns, Beauchaine, & Becker, 2016; Mullins, Bellgrove, Gill & Robertson, 2005).

The ADHD-IN vs. ADHDHI/C distinction is supported by considerable research showing different genetic, neural, and cognitive mechanisms, in addition to differences in type of inattention and risk for externalizing behavior (Beauchaine & McNulty, 2013). ADHD-IN is characterized by later age of onset, later age of referral, a different genetic profile, unique patterns of transmission across generations, hypoactivity, shyness, sluggish cognitive tempo (e.g., low motivation, drowsiness, lethargy), neglect by peers, and isolation. In contrast, ADHD-HI/C is characterized by restlessness, constant talking, trouble engaging, impatience, and lack of attention to consequences of actions. ADHD-HI/C in particular portends development of later, more severe externalizing behavior (Adams, Derefinko, Milich & Fillmore, 2008; McDonough-Caplan, Klien & Beauchaine, 2018). Finally, ADHD-IN and ADHD-HI/C show different patterns of resting state brain connectivity: whereas ADHD-HI/C is characterized by deficiencies in insular and midline connectivity, ADHD-IN is characterized by deficiencies in the cerebellar and dorsolateral prefrontal cortex (dlPFC) connectivity (Fair et al., 2013).

When discussing ADHD-IN and ADHD-HI/C, it is also important to consider large sex differences in the prevalence of ADHD-HI/C but not ADHD-IN. In both community and treatment-seeking samples, ADHD HI/C diagnoses are much more common in boys than girls (Brown et al., 2009; DuPaul, Schaughency, Weyandt, Tripp & Kiesner, 2001; Ghanizadeh, 2009;

Cahill et al., 2012). In contrast, ADHD-IN is diagnosed in roughly equal proportions by sex. As described above, growing evidence also suggests that girls and boys diagnosed with ADHD-HI/C follow different developmental trajectories. Whereas boys with ADHD-HI/C are vulnerable to later ODD, CD, delinquency, substance use, criminality, and ASPD into adulthood, girls with ADHD-HI/C are vulnerable to later ODD, self-harm behaviors, substance use, suicidal behaviors, and borderline personality development into adulthood (Beauchaine, 2020; Beauchaine et al., 2019). These sex-moderated developmental patterns are important to consider because much existing literature fails to dissociate mechanisms through which different ADHD presentations develop across the lifespan, obscuring our understanding of how the disorder leads to negative functional outcomes for boys vs. girls. In turn, this impedes effective prevention and treatment (Beauchaine et al. 2008).

It is important to emphasize that sex differences in ADHD are found even after controlling for various sources of measurement error, which could otherwise bias prevalence estimates. For example, Arnett, Pennington, Willcutt, DeFries, and Olson (2015) suggest that selection bias, lack of measurement invariance across sexes, and failure to measure certain symptoms could explain differences in observed prevalence rates. Selection bias is particularly problematic in clinically referred samples, where boys are heavily overrepresented. However, sex differences are still observed in community samples, where referrals are based on teacher- and parent-reports.

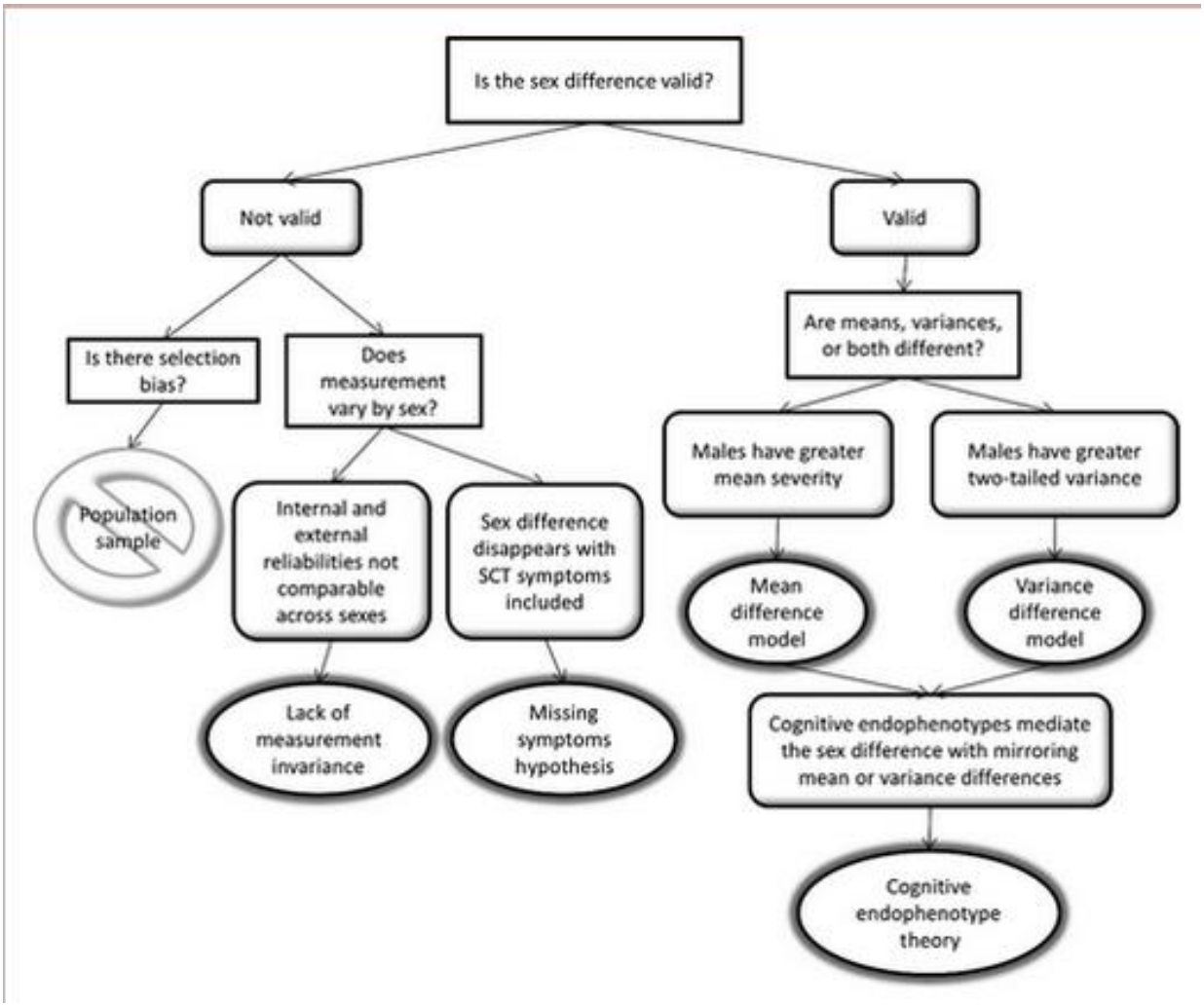
Relatedly, due to historic over-representation of boys, ADHD symptom criteria themselves may have been constructed with inherent sex bias, leading to ADHD measures/rating scales that differ in validity by sex. Yet in contrast to this hypothesis, measurement invariance across sex is established in both clinical and community samples (Arcia & Conners, 1998). Finally, the

sluggish cognitive tempo symptom cluster (characteristic of ADHD-IN) has traditionally not been measured when assessing ADHD, which could lead to under-representation of girls if they are more affected by such symptoms. However, including these symptoms in assessment produces the opposite effect, whereby boys' sluggish cognitive tempo severity is more severe than girls'. Collectively, these findings suggest that sex differences in ADHD are real. At present, the bases of sex differences are not fully understood. In the remainder of this paper, I consider mechanisms of sex differences in presentations of ADHD-HI/C where they exist.

Arnett et al. (2015) propose that differences in prevalence may derive from a general mean difference in symptom severity, a difference in variance of symptom severity, or both. If we assume that symptom severity of ADHD follows a normal distribution, and that we establish an arbitrary diagnostic threshold in the right tail of the distribution, a larger symptom mean (severity) and/or a larger variance (dispersion) of the normal distribution for boys relative to girls would lead to more boys falling over the diagnostic threshold. By recruiting twins and siblings, administering ADHD inventories, and cognitive testing, Arnett et al. (2015) showed that some combination of increased mean and variance best explained the discrepancy of ADHD between sexes (Arnett et al., 2015). Figure 2, included below, illustrates their method. Thus, mechanisms that give rise to ADHD in boys may differ from those that give rise to ADHD in girls. More detailed findings regarding sex differences in ADHD and related externalizing disorders can be found elsewhere (e.g., Eme, 2007; Eme & Kavanaugh, 2010).

Figure 2

Possible sources of sex differences in ADHD-HI/C. From Arnett et al. (2015).



Despite consistent sex differences in prevalence rates and developmental trajectories of ADHD, specific mechanisms remain underexplored. Notably, many if not most studies include both presentations and both sexes in single analyses, adding measurement error and obscuring subtype and sex differences. This has also resulted in single treatments (e.g., stimulants) being applied to all presentations, despite evidence of differential stimulant response (e.g., Stein, Sarampote, Waldman, Robb, & Conlon, 2003). Although stimulant effectiveness suggests dopaminergic mechanisms, we must explore how these mechanisms might differ in magnitude

and/or quality between sexes, rather than assuming invariance across sex.

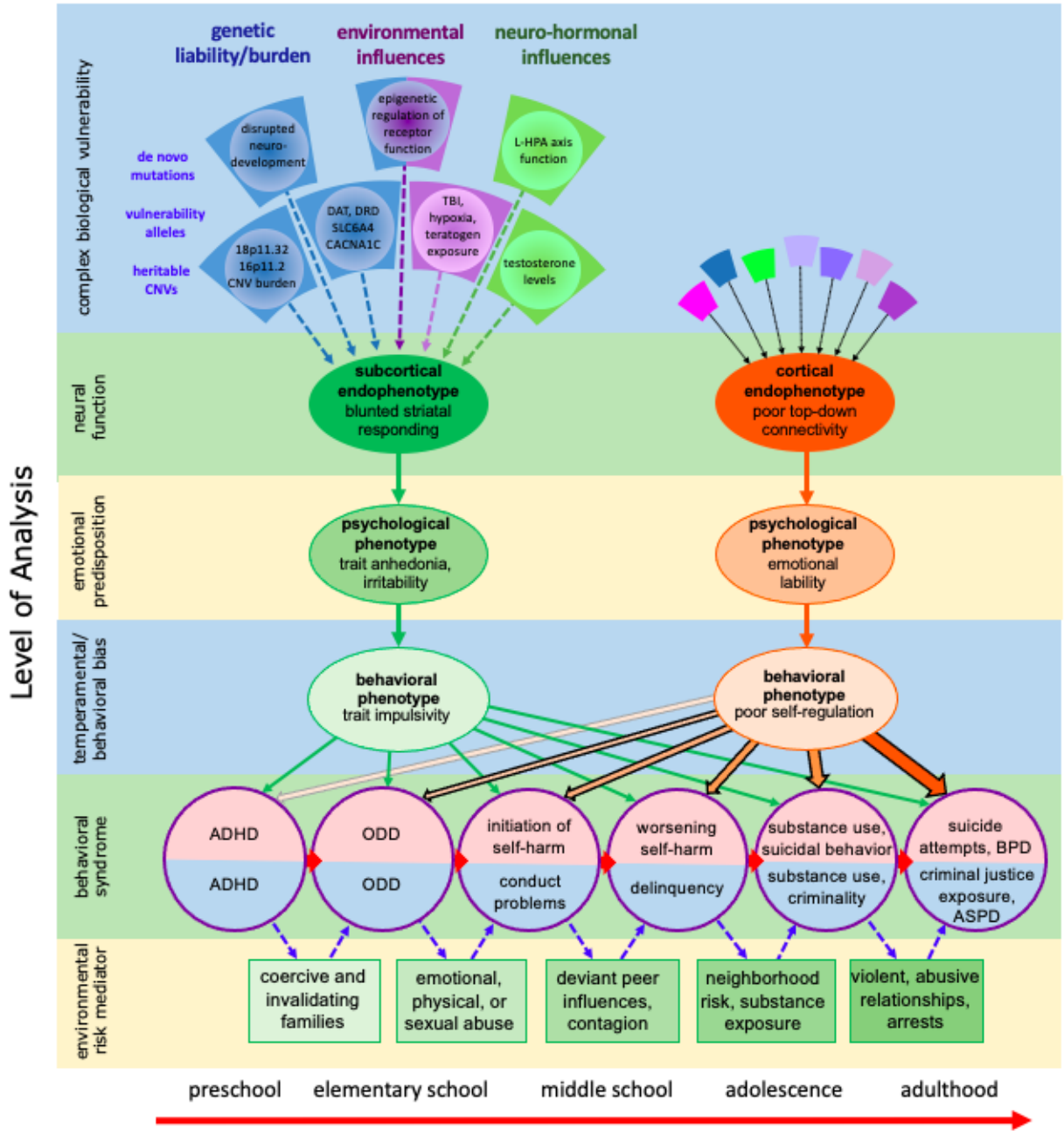
In this paper, I review sex differences in ADHD from a biopsychosocial perspective, which assumes that for some ADHD emerges and develops into more severe psychopathology through combinations of biological vulnerability and environmental risk (Beauchaine & Constantino, 2017). My goal is to identify where more research is needed. The remainder of this paper is organized as follows. First, I describe the ontogenic process perspective on externalizing psychopathology, with an emphasis on how ADHD sometimes develops differently for boys vs. girls across the lifespan. In describing this perspective, I focus on neural factors that play important roles in development of ADHD, and how these factors vary by sex. Second, I describe genetic, environmental, social, and cognitive factors that mediate sex differences in ADHD. I end by discussing gaps in literature, which could motivate future research.

The Ontogenic Process Perspective on Externalizing Psychopathology

Ontogenesis refers to processes through which biological attributes and environmental factors interact to shape neural and behavioral development across the lifespan (see e.g., Haines & Beauchaine, 2020). Below I provide a brief overview of Beauchaine and McNulty's (2013) model of externalizing psychopathology, which describes complex contributions of trait impulsivity, trait anxiety, executive function/emotion regulation, and neurodevelopment to progression of ADHD-HI/C to more severe externalizing disorders across the lifespan. As already noted, such progression often differs by sex (Beauchaine et al., 2013, 2017, 2019). It is also important to note that many children with ADHD-HI/C do not follow a progressive developmental trajectory. I focus here on those who do. Figure 3 depicts the entire ontogenic process perspective, including selected biological vulnerabilities depicting environmental risk factors that contribute to development of externalizing progression.

Figure 3

An ontogenic process model of externalizing development. From Beauchaine (2020).



Trait Impulsivity as a Core Vulnerability

According to the ontogenic perspective, trait impulsivity is a core vulnerability to ADHD-HI/C and all other externalizing disorders including ODD, CD, SUDs, and ASPD for boys/men;

as well as ADHD-HI/C, self-harm, suicide attempts, and BPD for girls/women. Trait impulsivity is a highly heritable, normally distributed temperamental vulnerability (Sagvolden, Johansen, Aase & Russell, 2005; Wingrove & Bond, 1997; Beauchaine et al., 2017, 2019; Perales, Verdejo-García, Moya, Lozano & Pérez-García, 2009; Neuhaus, E. M. I. L. Y., & Beauchaine, 2013; Velázquez-Sánchez, Ferragud, Moore, Everitt & Sabino, 2014). It is expressed early in the preschool years as temperamental surgency and core symptoms of ADHD-HI/C. In later childhood, adolescence, and adulthood, it manifests as lack of foresight, failure to plan ahead, and preference for immediate over delayed rewards. These symptoms reflect compromised self-control, which can lead to more maladaptive behaviors. This definition of trait impulsivity is supported by a single latent factor that underlies all behavioral symptoms, as seen in numerous factor analytic studies (Biederman, Faraone, Doyle, Lehman & Kraus, 1993; Biederman, Faraone, Keenan, Benjamin, Krifcher & Moore, 1992; Chen, Faraone, Biederman & Tsuang, 1994; Eaves, Silberg, Hewitt, Rutter & Meyer, 1993; Hudziak, Heath, Madden, Reich & Bucholz,, 1998).

According to the ontogenic process perspective, trait impulsivity is itself multiply determined by various person-level vulnerabilities, which interact with environmental risk factors across the lifespan to produce increasingly problematic patterns of impulsive behavior. Thus, symptoms of trait impulsivity derive from multiple underlying neural and environmental mechanisms (see Beauchaine & Constantino, 2017)—some of which may vary by sex as well as demographics (Eme, 2007). Direct attention to developmental processes is crucial when examining how ADHD and other externalizing psychopathologies develop.

Investigating specifical neural underpinnings of behavior is essential if we wish to understand etiology (e.g., Beauchaine et al., 2008). A core vulnerability to ADHD-HI/C is

deficient neural responding in the striatum and feed-forward projections to the PFC. (Beauchaine et al., 2017; Plichta & Scheres, 2014; Sagvolden, 2005). Haber and Knutson (2010) conducted an fMRI study investigating brain activity and reward-processing tasks. They found a consistent positive correlation between impulsivity-related measures and oxygenation levels (indicating neural activity) in the ventral-striatum (VS), a core component of the reward circuit. Sonuga-Barke (2003) elaborated on these implications for ADHD, finding that the dysregulation in the firing patterns of DA-mesolimbic cells underlies atypical response to reinforcement.

Self-Control

Self-control is indexed in various ways. In early childhood, a simple operationalization of impulsivity and related constructs such as self-control is the marshmallow test (Mischel, 2014; Gagne, 2017). This involves asking children to choose between one marshmallow now or two marshmallows later. This assumes that marshmallows are of value to participants, and two marshmallows are or of higher value than one. There is a decision involved; wait some time and receive a larger reward (delayed gratification) or receive the smaller reward without having to wait (immediate gratification). Impulsive children are more likely than non-impulsive children to choose one marshmallow now (Gagne, 2017).

Throughout this paper, the term “self-control” is used when referring to various aspects of impulsive behavior and impulsive decision-making. In a meta-analysis that surveyed facets of self-control (e.g., executive function, delay of gratification, self-reportd), the authors found support for a multi-dimensional assessment using various outcomes (functional, trait-level, cognitive, symptoms, age, memory, attention, and planning).

Studies conducted over the past 60 years have established that both subcortical and cortical brain structures and circuits are implicated in generating and inhibiting impulsive/excessive

approach behaviors (Boroojerdi, Diefenbach & Ferbert, 1996; Colcombe, Kramer, Erickson & Scalf, 2005; Rubia, Smith, Brammer & Taylor, 2003; Raine et al., 1998). Various brain regions are of course interconnected, and work together to subserve behavior. Thus, although each brain region and neural system must be considered, their interactive roles must also be discussed to understand ADHD (and other disorders). I consider such interactions below.

Executive Function and Emotion Regulation

Executive function (EF) comprises effortful attentional and cognitive process, including emotion regulation, described below, through which humans control their behaviors in the service of current and long-term goals. They are higher-order processes used to regulate behaviors, thoughts, and actions. EF is a multidimensional construct, including attention, working memory, inhibitory control, and planning (Gagne, 2017; Closson, 2010; Martel, Nikolas & Nigg, 2007). Core EF functions are required to organize behavior (e.g., Sagvolden et al., 2005). Compromises in EF are observed among those with high trait, including ASDHD, and among those who score high on trait anxiety (Ursache & Raver, 2014). Deficits in EF account for certain patterns of dysfunction among those affected by ADHD (Martel et al., 2007).

Emotion regulation (ER) comprises top-down executive processes that used to modulate emotional experience and expression (Gross, 1998; Landis, Garcia, Hart & Graziano, P. A., 2020). ER is therefore another a form of self-regulation. Studies show that many but not all children with ADHD suffer deficits in ER (e.g., Barkley, 2015; Graziano & Garcia, 2016), as expressed by difficulties suppressing feelings of frustration, anger, and impatience. Interestingly, some authors have found that ER is associated with hyperactivity in older children (Martel, Nigg & Lucas, 2008), but with inattention in younger children (Martel et al., 2008). This indicates the need to evaluate EF and ER developmentally.

As noted above, the maturation lag model posits that neurodevelopment of those with ADHD is similar to that of younger healthy children than to age-matched peers. Alternatively, the developmental deviation model suggests that ADHD derives from lifelong differences in brain function. Thus, neurodevelopmental profiles of those with ADHD is not comparable to normal brain profiles at any age. Finally, the cortical hypoarousal model suggests lower levels of cortical activity among those with ADHD vs. those without ADHD.

Trait Anxiety

Trait anxiety, which is characterized by shyness, passive avoidance of real and perceived threat, and wariness of novelty—is another temperament/personality dimension that influences how likely people are to engage in impulsive behaviors. In general, high trait anxiety is associated with worry, rumination, anxiety disorders, and neurobiological reactivity to external events (Endler & Kocovski, 2001; Spielberg, 1983; Peters, Bowen & Balbuena, 2020). When combined with trait impulsivity, low trait anxiety, which correlates strongly with callous-unemotional traits in children and adolescents, increases risk for externalizing progression (Beauchaine et al., 2017). Thus, trait anxiety can moderate the expression of impulsivity (Beauchaine et al., 2017). Modulation of impulsivity by anxiety is described in reinforcement sensitivity theory (RST) (Corr, 2008; Corr, McNaughton, Wilson, Hutchison & Burch, 2016). When cues in the environment conflict in motivational valence (approach vs. avoidance), ongoing behavior is suppressed by anxiety to help better arbitrate between risky options. Accordingly, trait anxiety predicts more deliberate responses to conflicts in the environment (e.g., Bloemsma et al., 2013; Haines & Beauchaine, 2020).

As noted above, other behavioral systems modulate impulsivity. For example, abnormalities in the septo-hippocampal system confer risk for anxiety and depression (Gray & McNaughton,

2000; Hajós, Hoffmann, Robinson, Jen & Hajós-Korcsok, 2003). Of course, it does not work in isolation from other external factors or neural networks but understanding that this specific brain region plays a role in the development in mood disorders can help understand one piece of the cause, and perhaps inform treatment methods. In the same way, we aim to investigate the neural correlates of sex difference in ADHD, to identify differences found in literature, and disparities that future research can address.

In the remainder of this paper, I discuss the neurobiology underlying sex differences by focusing on two important neural systems, one dopaminergic and the other largely serotonergic. While noradrenergic and cholinergic systems will be discussed briefly, they will be referred to in context of the first two systems. We begin discussion of the mesolimbic dopamine (DA) system, which has long been thought to play a role in the development and maintenance of ADHD.

Neurobiological Markers and Mechanisms of Vulnerability to ADHD

Electroencephalography

EEG is a form of electrophysiological recording that can measure both baseline (tonic) cortical activity and stimulus-elicited (phasic) cortical activity, using electrodes placed on the scalp. This provides indices of underlying brain state both before and during activation. Some EEG paradigms reveal statistical differences between those with ADHD vs. without. For example, participants with ADHD show higher levels of basal EEG theta activity (Mann, Lubar, Zimmerman, Miller & Muenchen, 1992).

EEG is also used to measure event-related potentials (ERPs), defined by phasic responses to either internal or (more often) external stimuli (Handy, 2005). It can be a useful measure of reward responsiveness and attention, providing insight into their temporal dynamics. One useful ERP is the error-related negativity (ERN)—a negative deflection in neural activity following

participants' errors during certain tasks. Liotti, Pliszka, Perez, Kothmann, and Woldorff (2005) compared ERPs elicited from typically developing children vs. children with ADHD. Children with ADHD showed smaller ERNs. This suggests either (a) that children with ADHD fail to notice their errors, or (b) they are less concerned about their errors.

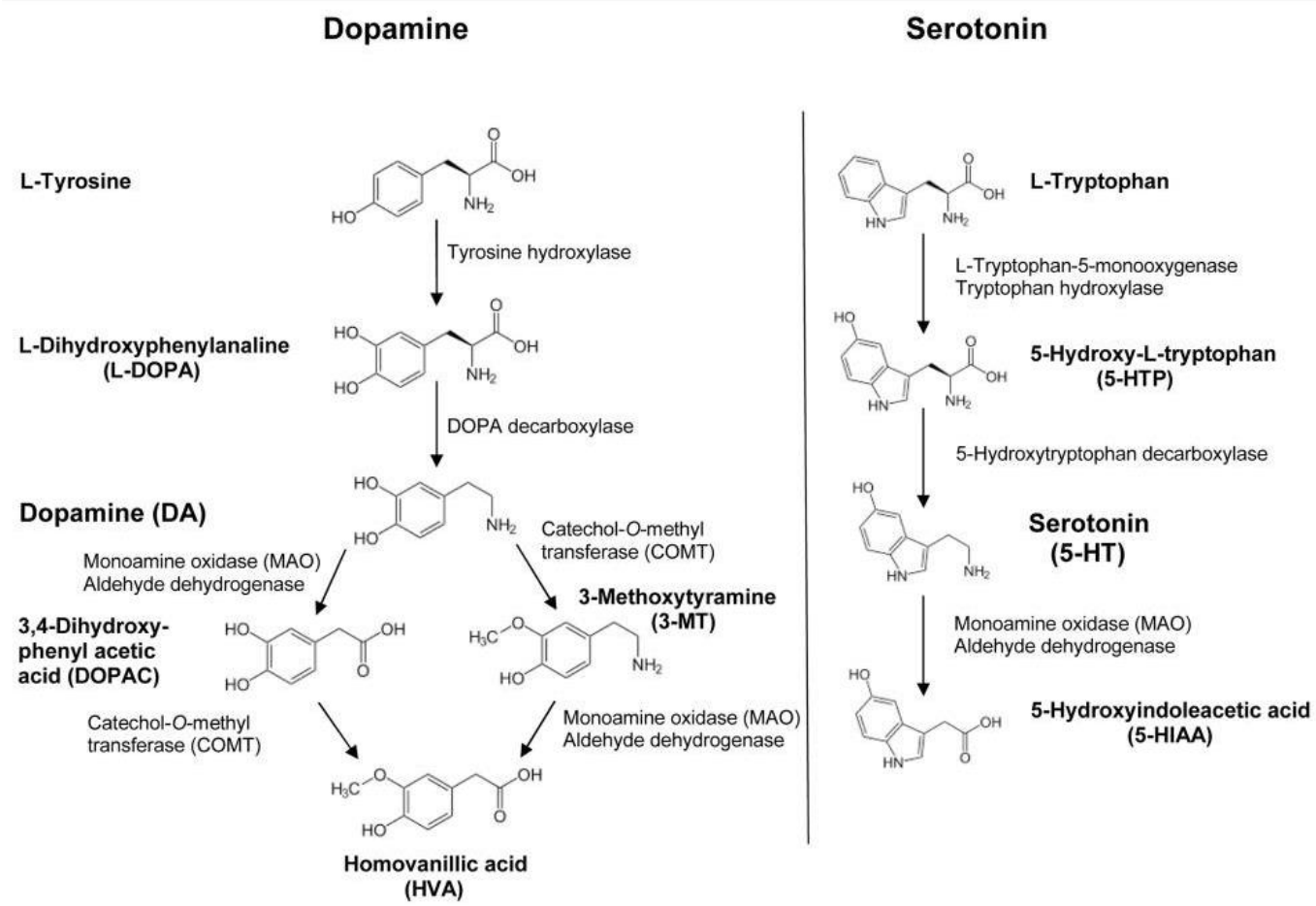
Electrodermal Activity (EDA) refers to changes in electrical across the skin. It is often used to index sympathetic nervous system arousal, and can indicate anxiety (or lack thereof). Three studies (Lazzaro et al., 1999, Hermens, Kohn, Clarke, Gordon & Williams, 2005 and Hermens et al., 2004) used EEG and electrodermal activity (EDA) simultaneously. In general, the entire group of adults with ADHD had deviations in SCL and EEG which were consistent with adolescents and children with ADHD. However, higher theta levels were present in males but not females with ADHD. Females with ADHD had lower skin conductance levels (SCL, an index of EDA) than males with ADHD. This finding was corroborated by Clarke (2001b) and Hermens et al. (2005), who explored the same outcomes in adolescent males and females with ADHD. These results suggest that the mechanisms that underpin ADHD might be disctinct.

Dopamine and Serotonin

In the rest of this paper, I review neurotransmitter systems involved in ADHD, including dopaminergic, serotonergic, and noradrenergic pathways. Understanding genetic, metabolic, and functional aspects of these systems provides insight into the complexity of self-control. For illustrative purposes, Figure 4 summarizes both DA and h-HT metabolic pathways, including both precursors and metabolites—expression of which is affected by genetic variation.

Figure 4.

Synthesis and metabolism pathways for serotonin and dopamine. From Beauchaine et al. (2009).



The Dopaminergic System and sex differences

Dopamine (DA) is a catecholamine neurotransmitter. There are several DA systems in the brain. Among these, the mesolimbic system, including projections from the nucleus accumbens to the dorsal and ventral striatum, is commonly referred to as the reward system (see e.g., Sagvolden et al, 2005). It is important to note, however, that this neural system is involved in all associative learning (e.g., Arias-Carrión, Stamelou, Murillo-Rodríguez, Menéndez-González & Pöppel, 2010). Among typically developing children, adolescents, and adults, DA

activity increases during anticipation and delivery of monetary rewards and other incentives (Dreher, Kohn, Kolachana, Weinberger & Berman, 2009).

Sagvolden et al. (2005) emphasize mesolimbic-mediated reward learning in their Dynamic Developmental Theory (DDT) of ADHD. They propose two mechanisms underlying ADHD: blunted reinforcement of novel behavior and deficient extinction of previously reinforced behavior. They argue that reinforcement and extinction are dynamically controlled by tonic and phasic dopamine activity, which can be influenced by a variety of factors including drugs, genetics, and environmental toxins. DDT suggests that a hypofunctioning mesocortical system results hyperactivity, impulsivity, poor behavioral organization, shorter-delay-of-reinforcement gratification, and deficient extinction learning. In contrast, a hypofunctioning nigrostriatal pathway from the substantia nigra to the striatum yields clumsiness and poor nondeclarative learning habits.

According to Sagvolden et al. (2005), blunted tonic DA activity among those with ADHD may result from diminished cortical modulation (inhibition) of midbrain DA neurons. Typically, tonic and phasic DA components are tightly regulated—the tonic phase modulates autoreceptors on DA terminals, thereby "gating" phasic DA release to reinforcing stimuli. Tonic DA levels are partly controlled by glutamatergic inputs from cortical regions. Therefore, an underdeveloped or hypofunctioning prefrontal cortex (often found in those with ADHD; Rubia et al., 2010) reduces top-down glutamatergic input, resulting in abnormally low tonic DA levels. These extremely low tonic DA levels cause a floor effect that artificially reduces the magnitude of negative prediction errors, giving rise to impaired extinction learning (Sagvolden et al., 2005).

Other research (Arias-Carrión et al., 2010; Schultz, 1997) looks at how the expectation and the consequent receipt of reinforcers evokes increase in DA (positive prediction errors). Indeed,

research shows that mesolimbic neural activity increases during reward-seeking and reward anticipation. It also increases after the delivery of DA agonists (compounds that activate dopamine receptors). The accompanying cognitive impulsiveness component results from the same short time span, resulting in less time to contemplate future plans, forgetfulness, and problems with organizing behavior (Sagvolden et al., 2005).Therefore, sex differences in subcortical development could play a key role in differences in impulsive behavior.

Reviews of neuroimaging literature indicate abnormalities in frontal and/or frontostriatal networks among this with ADHD, compared to controls. MRI studies shown reduced volumes of the total brain, corpus callosum, caudate and/or cerebellum. PET has also demonstrated reduced prefrontal cortex metabolism in adults. In adolescent girls specifically, hyperactive girls had a 17.6% lower absolute brain metabolism than typically developing girls (Ernst et al., 1994; Wilens, Biederman & Spencer, 2002).

Blunted DA responses might be caused by a multitude of things, but we focus on two aspects – insufficient glutamate released from the prefrontal cortex for the dopamine receptors, or faulty regulation of dopamine receptors. A large literature supports the idea that parts of the prefrontal cortex (PFC) plays a part in regulating impulsivity (Liu et al., 2019; Loos et al, 2014; Arnsten & Li, 2005). Studies have shown that impulsive behaviors are lined to activity in the orbitofrontal (represents emotion and reward in decision-making) and dorsolateral prefrontal (responsible for executive functions such as working memory, planning, and inhibition) inhibition of striatal activity (Berlin, Rolls & Iversen, 2005; Hariri et al., 2006), whereas anxiety is regulated in part through lateral and medial prefrontal inhibition of amygdalar activity (Rauch, Shin & Wright, 2003). As noted above, anxiety moderates impulsivity.

Research has explored the mesolimbic and cortical mechanisms in their impact on expression

of trait impulsivity, finding that the former play a relatively larger role in childhood, while the latter takes on greater importance later in development (via emotion dysregulatory effects), during adolescence and adulthood (Sharkley et al., 2019). Emotion dysregulation is correlated with development of aggressive behavior across adolescence as well (Muratori, Pisano, Milone, & Masi, 2017). Therefore, differences in cortical maturation between boys and girls could play a large role in differential expression of impulsivity at the behavioral level.

Furthermore, DA antagonists eliminate motivation to use stimulants and drugs of abuse by blocking the rewarding properties of the aforementioned and primary reinforcers (Chiara, 1995). This led to the idea that the mesolimbic structures of the brain are linked to impulsivity, reward-seeking and extraversion (Depue & Collins, 1995). Furthermore, the mesocortical structure provides inhibitory control over the mesolimbic activity, increasing as the individual ages (Kabanova et al., 2015).

Studies have also shown that low levels of striatal/mesolimbic DA activity and reactivity are associated with trait irritability. This chronically irritable mood state provides motivation to elevate mood by engaging in reward and novelty seeking behaviors (Depue et al., 1994). Further modern neuroimaging research in the past decade has revealed compromised functional connectivity between the mesolimbic and mesocortical structures among adolescents with ADHD and other CDs. An fMRI study (Scheres, Tontsch, Thoeny & Kaczkurkin, 2010) found that children and adolescents showed blunted mesolimbic neural reactivity to reward compared to controls, regardless of whether they had comorbid conduct problems or not.

On a behavioral level, the consequences of hypofunctioning DA system influences the temporal domain, in effect influencing how much the child with ADHD can adjust behavior to specific timeframes (motor timing), perceiving and estimating timeframes (time

estimation/discrimination), and considering the future consequences of behavior (temporal foresight). These timing functions are interrelated, working together to produce the most adaptive behavior (Noreika, Falter & Rubia, 2013).

Abnormalities in any of these timing functions could result in abnormal behavior. Children with ADHD, a disorder characterized by impulsivity, tend to show symptoms that align with these temporal abnormalities. I will be focusing on the third function in my research, temporal foresight. Studies investigating brain regions involved in temporal foresight, using neuroimaging techniques such as lesion studies and fMRI, found that fronto-striatal and ventromedial prefrontal brain regions both seem to be involved. This study concludes by stating that fMRI data seems to indicate that different, overlapping neural networks work cooperatively to mediate timing functions (Rubia, 2006).

This study (Andersen & Teicher, 2000) investigated gender differences in the production and elimination of dopamine (DA) receptors in the striatum and nucleus accumbens. By dissecting brain of male and female rats of different ages, the researchers found that there was a significant difference in patterns of dopamine receptor development, across perioadolescence. They hypothesized that the overproduction and subsequent extensive pruning (after puberty) aligns with the development of symptoms of ADHD pre-pubescently, and the decline in symptoms post-pubescently in males. Another study showed that female dopamine receptor density declined at a slower rate than males. This data supports differences in brain structure between sexes, perhaps supporting how symptoms of ADHD manifest differently between the sexes (Andersen et al., 2000).

Zhang and Cohn (2011) conducted an animal study on rats, administering testosterone to rats, looking at hyperactivity, abnormal stress responses, and dopaminergic dysfunction in the

frontal cortex. They found that these behaviors increased drastically in young, ADHD-prone male rats, while it was not a prevalent effect in female rats. A possible mechanism for this effect might be that testosterone levels upregulate the expression of ADHD-associated genes (MAOA, COMT, and TH) in dopamine-rich regions. Furthermore, Anderson and Teicher (2000) found an overproduction of DA receptors (specifically, D_1 and D_2) in striatum and accumbens through autoradiography. Both these studies could explain the uptick in hyperactive activity during adolescence in males, when the amount of testosterone and dopamine increase tremendously.

The expression of the sex-linked gene, SRY, may also indicate the role of DA as a moderator of impulsive behavior. SRY is a Y-linked gene, so is male specific. It has been recently understood to be a transcriptional regulator in the brain. It encodes a protein that leads to the production of genes previously mentioned to be linked with testosterone levels and ADHD symptoms, TH and MAOA. SRY's mediation of testosterone levels supports the DA dysregulation seen in males rather than females. Trent and Davies (2011) posit that if SRY does mediate impulsivity, females with Swyer syndrome (commonly lack SRY gene) might display abnormalities. This is an area that can be further researched to provide evidence for sex difference pathways.

The Serotonergic System and sex differences

Serotonin modulates dopamine transmission by acting on frontal-subcortical circuits (Feifel, 1999). Internalizing symptoms have been linked primarily to 5-HT-mediated septo-hippocampal function (Gray & McNeughton, 2000). Dopamine systems are anatomically linked to the serotonergic (5-HT) neuromodulator systems (which originate in the brainstem raphe nuclei). Reductions in the activity of the aforementioned systems have been linked to poor impulse control and aggressive behavior (Zepf et al., 2008). A mechanism proposed by various

researchers is that serotonin imbalances contribute to dopaminergic imbalances, which in turn, impact levels of impulsivity.

A study (Duchesne, Dufresne & Sullivan, 2009) conducted on rats investigating the differences in levels of serotonin and DA in both genders, finding that females have higher monoamine tissue content, while males have higher levels of metabolites, implying that the latter might just utilize more 5-HT and DA, through higher rates of release and reuptake. However, the researchers found that female rats release more DA than males in response to electrical stimulation. This accounts for the higher tissue content of neurotransmitter, but the lower metabolite levels are still not explained. Some studies report that estrogen reduces DA reuptake. Similarly, females have been shown to have higher concentrations of 5-HT in several brain regions. Other human imaging studies have shown that males have a much higher 5-HT synthesis rate.

When considering the menstrual cycle of women, premestrual symptoms (PMS) are known to intensify ADHD symptoms. This is theorized to be due to the drop in estrogen levels, which accompany a drop in dopamine levels. The 5-HT_A receptor plays a role in this change. Taken all together, the reduction in DA and serotonin levels during menstruation may explain the gender effect in development of comorbid disorders – female hormone variation likely underlies the tendency to develop depression and anxiety. Biver, Lotstra, Monclus, Wikler & Damhaut (1996) took the menstrual cycle-induced variations in the serotonergic system into account, finding that males still displayed a considerably higher level of variability (due to the aforementioned higher synthesis rate). This was linked to higher levels of impulsivity and aggression. This might account for some of the ADHD symptom differences between men and women.

Robert Oades (2007) separates impulsivity into cognitive (distractibility, failure to consider consequences, and losing things) and behavioral (temper tantrums, aggression, and disruption). While we will not employ these distinctions in our paper, it is important to consider them in the scope of this study – it seems that cognitive impulsivity lines up with inattention, while behavioral impulsivity lines up with hyperactivity. Research studies in knockout mice demonstrated a sex-linked difference in 5-HT baselines. Jones & Lucki (2005) found that female 5-HT_{1B} receptor knockout mice demonstrate a higher level of disinhibition of 5-HT release, which led to higher levels of hippocampal 5-HT. Oades found that low levels of 5-HT correlate with behavioral impulsivity, while high levels of 5-HT correlate with cognitive impulsivity, supporting the idea that serotonergic dysregulation contributes to differences between symptoms in men and women.

The Adrenergic System and sex differences

The adrenergic system concerns the neurotransmitters adrenaline (epinephrine) and noradrenaline (norepinephrine). This system is an important modulator of synaptic transmission in the nervous system. Adrenaline functions relate to anxiety and arousal, while noradrenaline participates in the sympathetic nervous system (part of the autonomic nervous system), playing a role in the development of cardiovascular diseases (ex: hypertension, cardiac arrythmias). Research has also shown that noradrenergic projections to the prefrontal cortex improve working memory through postsynaptic alpha2 receptors. Drugs used to treat ADHD target the prefrontal cortex, in areas where noradrenergic receptors work, providing support for the role of the adrenergic system in ADHD symptoms. This system is discussed in relation to DA, as it is a precursor of noradrenaline.

The previously discussed Cortisol Hypoarousal model is supported by the difference in expression of symptoms of ADHD between the sexes. Researchers have noted that extreme levels of tonic activity (specifically in the locus coerueus (LC)) correlate with poor task-related attention. The LC generates states of arousal, mediating attentional processes in the cortex. Feedback from the adrenergic system in important in resetting the LC to normal levels. The theta increases in males with ADHD may reflect this noradrenergic dysfunction, by the way of too much tonic activity. In contrast, females with ADHD, who experience little to none, and more localized, theta enhancement may reflect an LC feedback deficit. Both LC levels dysregulation in males and females reflects a dysfunction in the adrenergic systems.

Social and Environmental Moderators of Impulsivity

Social and Environmental Factors

The variation in neurobiology discussed so far influences how children make decisions and learn from the consequences of their behaviors, meaning that the environment within which a child is behaving plays a large role in the development of impulsive patterns of behavior. There are various environmental (social) factors which impact the development of ADHD, and further progression along the externalizing spectrum. It seems to begin with ineffective parenting (maternal aggression, parental warmth, and low empathetic awareness are some factors supported by previous research) and coercive family relationships (characterized by negative reinforcement), which predict aggressive behavior and generalization of harmful behaviors to peer groups (Beaucahine et al., 2017; Mokrova, O'Brien, Calkins & Keane, 2010; Kaiser, McBurnett & Pfiffner, 2011; Lindahl, 1998). Within peer groups, deviant peers and neighborhood characteristics (such as availability of criminal opportunities, socioeconomic status, drug availability and use) are factors that mediate impulsivity and externalizing outcomes.

(Ortal et al., 2015; Marshal, Molina & Pelham, 2003; Marshal & Molina, 2006). It is also important to note that those higher in trait impulsivity are more vulnerable to substance abuse, as stimulants can increase nucleal firing in mesolimbic structures, providing temporary relief from chronically aversive mood states. (Loree, Lundahl & Ledgerwood, 2015; Holmes, Hollinshead, Roffman, Smoller & Buckner, 2016).

Neurodevelopment, Genetics x Environmental Factors

In addition to neurobiology influencing behavior, behavior can in turn influence neurobiology. Impulsive behaviors can impact the development of the frontal region (previously discussed as a key structure in moderating trait impulsivity and trait anxiety), through neurodevelopmental processes like neural plasticity, pruning, and programming. This can in turn influence the developmental of brain regions that mature later, such as the prefrontal area. Research has shown that children with ADHD and CD experience cortical thinning and reduced gray matter density in this area (Beauchaine et al., 2017). Epigenetics, which addresses the situation when DNA structure is altered by environmental experience, may also play a role in impulsivity. Animal studies show that DA neurons within the mesolimbic structures are susceptible to environmental regulation, as is the PFC. Prolonged use of stimulants has been found to alter cortical and subcortical function, suppressing strength of connection. Additionally, chronic stress has been found to affect long-term function of subcortical and cortical DA systems (in rats).

Previous research supports the idea that genetics might underlie this relation of impulsivity to DA function . While effect sizes for individual genes are small, there are still significant genetic associations between ADHD, CDs and various combinations of the same. This is seen in DA receptors (DRD4, DRD5), DA transport 1 gene (DAT), the monoamine

oxidase A gene (MAOA), and the catechol-O-methyltransferase gene (COMT). There are also genetic correlates of the serotonin system (certain genes of note are the HTR1B serotonin receptor gene and the 5-HTTLPR gene). While there is a small effect size for the variance of these genes, the interaction with environmental factors determines the risk of expression and vulnerability (Beauchaine et al., 2017). Hence, genetics influence neurobiology, which in turn impacts behavior, which eventually impacts neurobiology, in a bidirectional cycle.

Implications

This literature review details initial evidence for neurochemical underpinnings of sex differences in ADHD. The Dopaminergic, Serotonergic, and Adrenergic systems all play a role in altering mechanisms of symptom expression in males and females, in conjunction with other factors such as age, society, genetics, and environment. While this paper took information from a wide range of sources, there were very few studies comparing both genders with ADHD (with similar symptom expression, rather, most had the same subtype, which does not confer identical symptoms). This was a limitation of this paper, and an avenue for improvement – a larger knowledge base of data must be acquired, looking at males and females while contrasting various factors (in line with the Ontogenic perspective), to guarantee a thorough investigation.

Furthermore, more research exploring ADHD specifically in girls is required. Currently, ADHD in boys is overrepresented in clinical populations, clinical referrals, and literature. Looking at ADHD in girls in isolation will allow us to fully understand the expression of symptoms prior to comparing it with boys. This might require the alteration of diagnostic material, or the creation of new diagnostic material that can assist more accurate diagnoses of both genders. This will also aid research into alteration of treatment methods (namely,

medication that works based on specific neural mechanisms), so they are better suited to the neural mechanisms of each gender.

During this literature review, specific research into longitudinal hormone changes would have also given us more insight into the progression of children with ADHD along externalizing or internalizing pathways. Hormones investigated in this review, such as estrogen and testosterone might be explored from a developmental perspective in those with ADHD at a deeper level, as some findings of this paper indicated a correlation.

There was also a lack of cross-cultural research into ADHD symptomology. This is another area that could be explored, and provide more insight into socio-cultural factors. Perhaps differences in gender treatment between cultures might portend different brain development, and hence, differences in ADHD expression!

Finally, a large scale implication of this research indicates that due to sex differences, women with ADHD tend to have higher rates of adolescent pregnancy and drug abuse. Implications can be explored in prenatal and parenting behaviors of women, to investigate how motherhood and familial relationships might be affected. Gaining more information about ADHD in women is one step in understanding the disorder as a whole better, in terms of research, diagnosis, and intervention efforts.

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